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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/854,825	05/12/97	CHISARI	F 329368-1010

HM21/1208

LEYDIG VOIT AND MAYER
TWO PRUDENTIAL PLAZA
180 NORTH STETSON SUITE 4900
CHICAGO IL 60601-6780

EXAMINER	
PARKIN, J	
ART UNIT	**PAPER NUMBER**
1648	8

DATE MAILED: 12/08/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

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ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents.

Responsive to Communication filed _____.

The enclosed is a correct copy of a reference relating to the last Office action. The correction is indicated below.

THE PERIOD FOR RESPONSE OF 3 MONTHS SET IN SAID OFFICE ACTION IS RESTRATED TO BEGIN WITH THE DATE OF THIS LETTER.

PART I CORRECT REFERENCE CITATION: Remailed Office dated 12/8/98. Office action was mailed To wrong address.

PART 2 CORRECT REFERENCE FURNISHED:

Donna Chapman,
Team Leader II, Group 1800

Office Action Summary	Application No. 08/854,825	Applicant(s) Chisari et al.
	Examiner Jeffrey S. Parkin, Ph.D.	Group Art Unit 1648

☒ Responsive to communication(s) filed on *23 Sep 1998*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *22-25, 30, 32, 36, 40, and 44-64* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *22-25, 30, 32, 36, 40, and 44-64* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Detailed Office Action

Status of the Claims

1. Acknowledgement is hereby made of the Amendment submitted 23 September, 1998, wherein claims 26-29, 31, 33-35, 37-39, and 41-43 were canceled without prejudice or disclaimer, claims 22-25, 30, 32, 36, 40, 44, 51, 52, 56, and 58 amended, and new claims 60-64 submitted. Claims 22-25, 30, 32, 36, 40, and 44-64 are pending in the instant application.

35 U.S.C. § 112, First Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 22-25, 30, 32, 36, 40, and 44-64 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). Applicants have included the limitation "no more than a total of two substitutions, deletions, or insertions" which does not receive adequate support in the disclosure. While the disclosure provides a general description pertaining to the manipulation of the claimed peptides (i.e., see p. 14 of the specification), it does not provide any support for

peptides having no more than two substitutions. However, there does appear to be support for peptides containing single amino acid substitutions, deletions, or insertions (see p. 14, lines 21-25). Applicants may obviate the rejection by including this limitation in the claim language.

4. Claims 22-25, 30, 32, 36, 40, and 44-64 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants have amended the claim language to include a limitation specifying that the peptides of interest contain "no more that a total of two substitutions, deletions, or insertions" in the CTL epitope.

Applicants traverse and submit, *inter alia*, that only routine experimentation would be required to practice the claimed invention. It was argued that the specification provides the requisite HCV CTL peptidic core structures, adequate guidance pertaining to the generation of suitable peptidic variants, and an appropriate screening assay for identifying peptides with the desired activity. Applicants further note that inoperative embodiments are permissible under the law provided that routine experimentation is all that is required to practice the claimed invention. Applicants' arguments have been thoroughly considered but are not deemed to be persuasive for the reasons of record set forth in Paper No. 5 and as further elaborated below.

In response to applicants' arguments, the Examiner does not dispute the assertion that *in vitro* screening assays are available to assess the CTL activity of any given peptide of interest. The crux of the rejection is directed toward the failure of the disclosure to provide adequate guidance pertaining to those amino

acid substitutions, additions, and deletions, and suitable flanking sequences, that will preserve the desired properties of any given peptide. Contrary to applicants' assertions, the prior art teaches that the molecular determinants governing CTL peptide processing, presentation, and recognition are poorly defined and that mutations and flanking regions in CTL epitopes can affect the properties of the peptide in an unpredictable manner (Smith *et al.*, 1997; Bertoletti *et al.*, 1994; Johnson *et al.*, 1992; Couillin *et al.*, 1995; and, Hahn *et al.*, 1992; Del Val *et al.*, 1991; Hahn *et al.*, 1992; and, Eisenlohr *et al.*, 1992). Furthermore, in order to practice the claimed invention, the skilled artisan would be required to synthesize and screen an excessive number of peptides (i.e., considering only single amino acid substitutions in the decameric peptide having SEQ ID NO.: 2, 19^{10} different peptides would have to be generated and tested) without having any ideal as to which peptides would be reasonably expected to have the requisite CTL activities. As previously noted, the art teaches that the mere presence of an MHC class I binding motif in a peptide is not sufficient to confer binding to the appropriate class I molecule (Nayersina *et al.*, 1993; Bertoletti *et al.*, 1994; Couillin *et al.*, 1995; and, Eisenlohr *et al.*, 1992). Finally, as previously noted, the art teaches that the capacity of a putative CTL epitope to bind to a class I molecule does not mean that the epitope will be immunogenic (Nayersina *et al.*, 1993; Couillin *et al.*, 1995; and, Eisenlohr *et al.*, 1992). The specification is silent concerning this caveat. Accordingly, when all these factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention. Applicants have only extended an invitation to the skilled artisan to perform further undue experimentation to ascertain which peptidic variants will have the desired immunological properties.

5. Claims 58 and 59 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn toward pharmaceutical compositions comprising HCV-derived peptides. Applicants traverse and submit that the claimed compositions have a credible utility as required under the guidelines set forth by the Patent and Trademark Office. Applicants suggest that a vigorous HCV-specific CTL response need not be demonstrated and that clinical efficacy of the claimed compounds is within the purview of the Food and Drug Administration, and not the PTO. Applicants' arguments have been thoroughly considered but are not deemed to be persuasive for the reasons of record in Paper No. 5 and as further elaborated below.

Applicants are reminded that the term pharmaceutical has an art-recognized definition and pertains to the use of medicinal drugs to treat disease (refer to Dorland's medical dictionary, 1988, pp. 1271-1272; *In re Gardner*, 166 U.S.P.Q. 138-142 (1970 C.C.P.A.); and, *Ex parte Skuballa*, 12 U.S.P.Q.2d 1570 (1989 Bd. Pat. App. Int.)). As such, there must be a reasonable nexus that would lead the skilled artisan to conclude, based upon the teachings of the specification, that the claimed CTL epitope-containing peptides would produce some sort of ameliorative effect pertaining to the clinical sequelae associated with HCV infection. This nexus is generally provided by performing *in vitro* experimentation and *in vivo* testing in a suitable experimental animal model that is reasonably predictive of clinical success. The disclosure describes the identification of several HCV CTL epitopes and cell lines specific thereto. However, the disclosure fails to describe any studies involving the claimed peptides that were performed in

a suitable animal model or provide appropriate references demonstrating that the *in vitro* assays employed are reasonably predictive of clinical efficacy.

Moreover, as previously set forth, the Examiner has already identified a number of additional pragmatic scientific caveats that would preclude the skilled artisan from practicing the claimed invention (i.e., (1) The art teaches that mutations in CTL epitopes adversely affect binding to the appropriate MHC Class I molecule; (2) The prior art teaches that flanking amino acid residues critically influence the degree of peptide processing and presentation; (3) The art teaches that the presence of an MHC class I binding motif in a peptide is not sufficient to confer binding to the appropriate class I molecule; (4) The art teaches that the capacity of a putative CTL epitope to bind to a class I molecule does not mean that the epitope will be immunogenic; (5) The art teaches that virally infected patients contain CTL epitopic variants with reduced HLA and T cell receptor binding capacities; (6) The art teaches that natural sequence variation in viruses, particularly in CTL epitopes, results in the generation of immune resistant viruses; (7) The art teaches that HCV-specific CTL may actually contribute to liver disease pathogenesis in chronically infected patients). Applicants' response fails to provide sufficient objective scientific evidence addressing these issues.

Additional literature was cited illustrating a number of other concerns (i.e., (1) The art teaches that patients chronically infected with HCV develop HCV-specific CTL, but these CTL response are unable to clear the infection or produce any immediate salubrious effects (Rehermann *et al.*, 1996); (2) The art teaches that a number of hurdles (i.e., the correlates of protective immunity are unknown; patients develop HCV-specific CTL responses that are inadequate and incapable of clearing viral infection) remain to be overcome before adoptive immunotherapy will become a

reality in the treatment of HCV infection (Koziel *et al.*, 1997; Koff, 1993; Prince, 1994); (3) The art teaches that appropriate *in vitro* and *in vivo* assays and systems are currently not available to the virologist pursuing HCV antivirals (Koff, 1993; Prince, 1994); and (4) The art teaches that suitable animal models are not currently available to the skilled artisan trying to develop an anti-HCV compound (Koff, 1993)). Thus, the skilled artisan would reasonably question the ability of the claimed compounds to function as efficacious therapeutics, absent the presentation of suitable experimental evidence to the contrary.

35 U.S.C. § 112, Second Paragraph

6. The previous rejection of claims 22-59 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is hereby withdrawn in response to applicants' amendment.

7. Claims 22-25, 30, 32, 36, 40, and 44-64 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended the claim language to recite that the claimed CTL epitopes contain "no more than two substitutions, deletions, or insertions at the corresponding amino acid positions" which is confusing. It is not readily manifest if the claim is directed toward peptides having amino acid substitutions, deletions, or insertions at a specific location within any given peptide or if the claim language refers to some other manipulation. Appropriate clarification is required.

Statutory Type Double Patenting, 35 U.S.C. § 101

8. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. § 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor . . ." Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S.P.Q. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 U.S.P.Q. 330 (C.C.P.A. 1957); and *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970).

A statutory type (35 U.S.C. § 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer **cannot** overcome a double patenting rejection based upon 35 U.S.C. § 101.

9. The previous rejection of claims 27, 29, 31, 33, 35, 37, 39, 41, and 43 under 35 U.S.C. § 101 as claiming the same invention as that of claims 2-10, respectively, of prior U.S. Patent No. 5,709,995, is hereby withdrawn in response to applicants' amendment.

Non-statutory Double Patenting

10. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum*, 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman*,

29 U.S.P.Q.2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

11. Claims 22-25, 30, 32, 36, 40, and 44-59 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 11-33 of U.S. Patent No. 5,709,995. Applicants have indicated that a terminal disclaimer will be submitted upon the identification of allowable subject matter.

Finality of Office Action

12. Applicant's amendment necessitated any and all new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR

RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Correspondence

13. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

14. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Chris Eisenschenk, J.D., Ph.D., can be reached at (703) 308-0452. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

04 December, 1998

LAURIE SCHEINER
PRIMARY EXAMINER